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PATHOLOGIC BASIS of DISEASE

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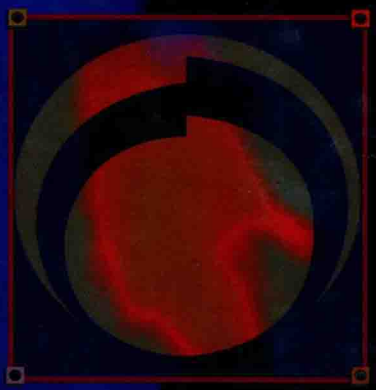

• Sixth Edition

Robbins

PATHOLOGIC BASIS of DISEASE

Sixth Edition

Ramzi S. Cotran, M.D.
Frank Burr Mallory Professor of Pathology
Harvard Medical School
Chairman, Department of Pathology
Brigham and Women's Hospital
The Children's Hospital
Boston, Massachusetts

Vinay Kumar, M.D., F.R.C.Path.
Vernie A. Stembridge Chair in Pathology
Department of Pathology
The University of Texas
Southwestern Medical School
Dallas, Texas

Tucker Collins, M.D., Ph.D.
Professor of Pathology
Harvard Medical School
Pathologist
Brigham and Women's Hospital
Boston, Massachusetts

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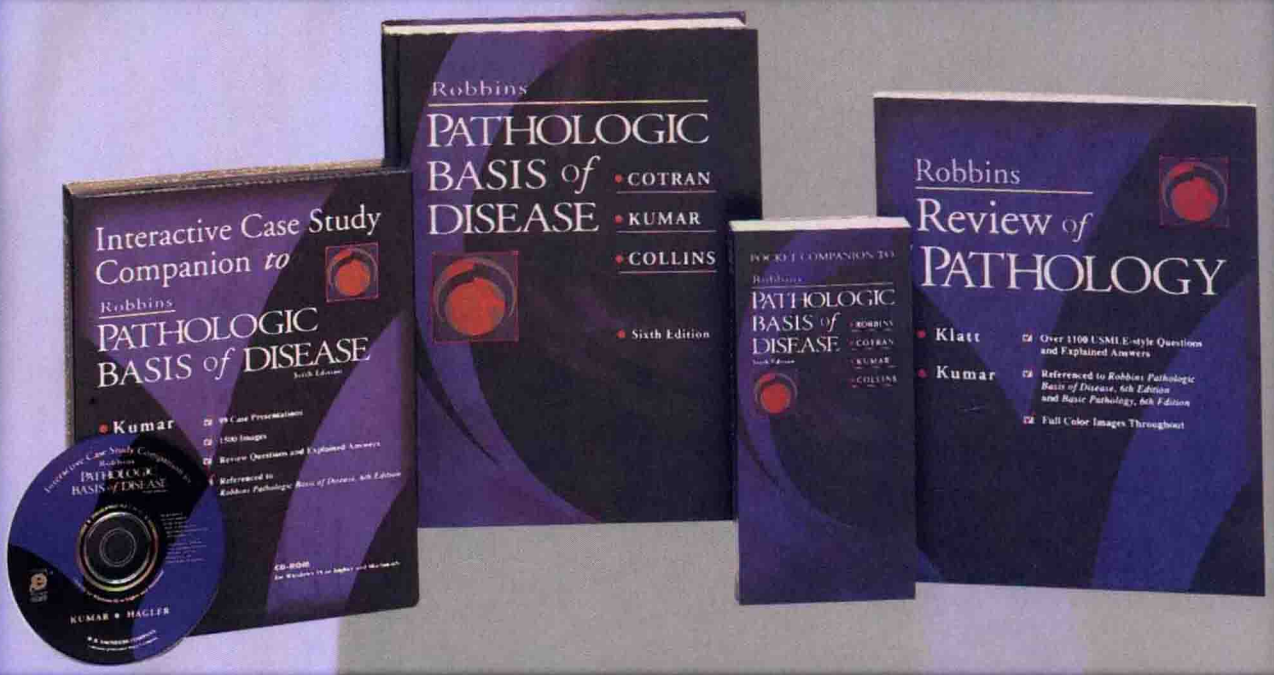

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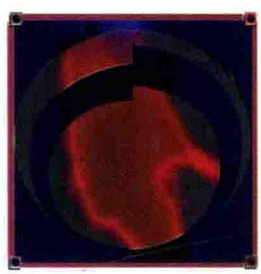

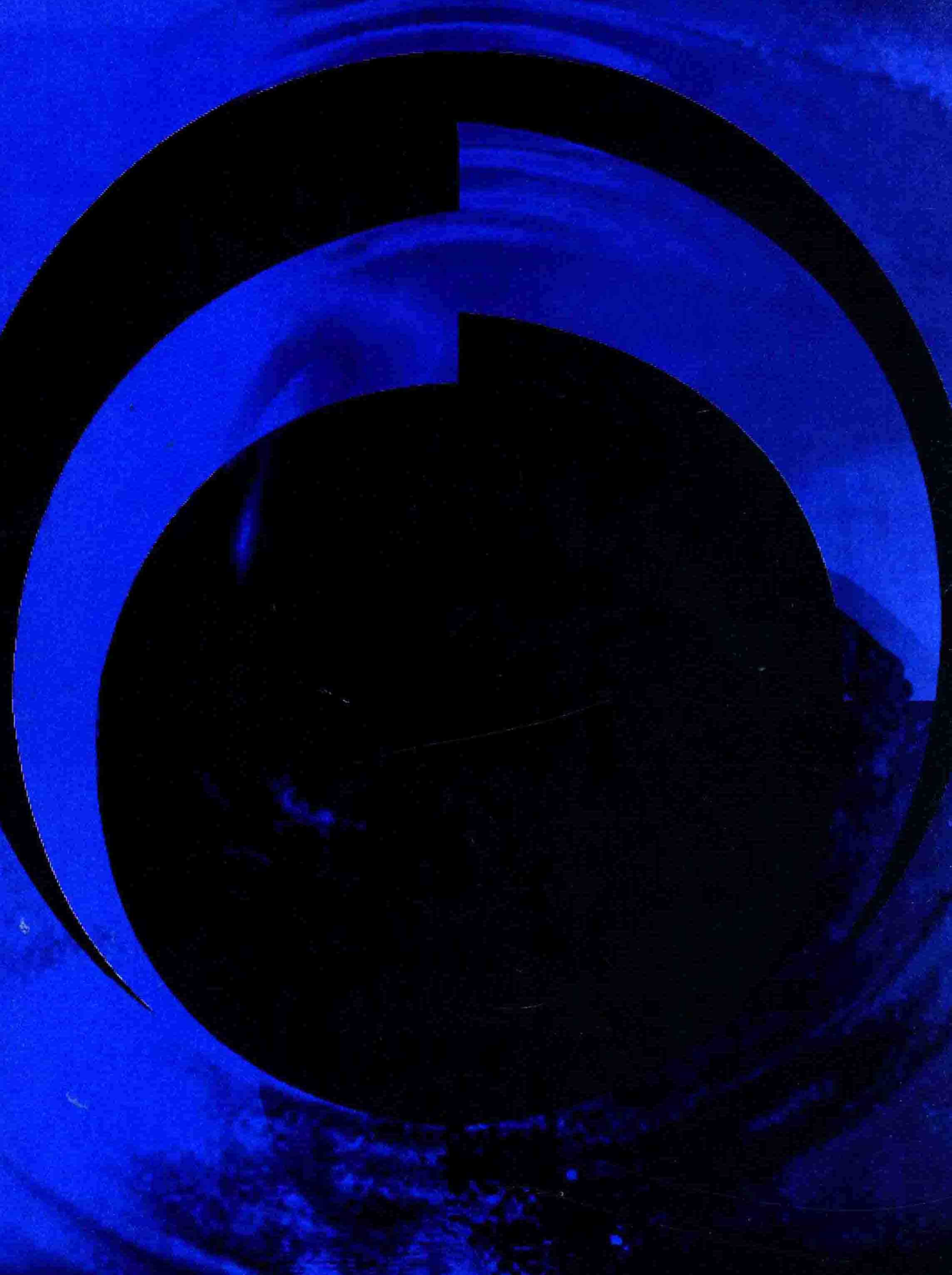

To Kerstin

To Raminder

To Mary

With love.

Contributors

Daniel M. Albert, M.D., M.S.
F.A. Davis Professor and Chair, Department of Ophthalmology and Visual Sciences, University of Wisconsin Medical School, Madison, WI
The Eye

Douglas C. Anthony, M.D., Ph.D.
Associate Professor of Pathology, Harvard Medical School; Director of Neuropathology, Children's Hospital, Boston, MA
Peripheral Nerve and Skeletal Muscle; The Central Nervous System

Jon Aster, M.D., Ph.D.
Assistant Professor of Pathology, Harvard Medical School; Pathologist, Brigham and Women's Hospital, Boston, MA
White Cells, Lymph Nodes, Spleen, and Thymus

James M. Crawford, M.D., Ph.D.
Associate Professor of Pathology, Director, Program in Gastrointestinal Pathology, Yale University School of Medicine, New Haven, CT
The Gastrointestinal Tract; The Liver and the Biliary Tract; The Pancreas

Christopher P. Crum, M.D.
Professor of Pathology, Harvard Medical School; Director, Women's and Perinatal Pathology, Brigham and Women's Hospital, Boston, MA
The Female Genital Tract

Umberto De Girolami, M.D.
Associate Professor of Pathology, Harvard Medical School; Director of Neuropathology, Brigham and Women's Hospital; Neuropathologist, Children's Hospital, Boston, MA
Peripheral Nerve and Skeletal Muscle; The Central Nervous System

Thaddeus P. Dryja, M.D.
David Glen Denning Cogan Professor, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA
The Eye

Matthew P. Frosch, M.D., Ph.D.
Assistant Professor of Pathology, Harvard Medical School; Neuropathologist, Brigham and Women's Hospital, Boston, MA
Peripheral Nerve and Skeletal Muscle; The Central Nervous System

Agnes B. Kane, M.D., Ph.D.
Chair and Professor, Department of Pathology, Brown University School of Medicine, Providence, RI
Environmental and Nutritional Pathology

Lester Kobzik, M.D.
Associate Professor of Pathology, Harvard Medical School; Pathologist, Brigham and Women's Hospital, Boston, MA
The Lung

Susan C. Lester, M.D., Ph.D.
Assistant Professor of Pathology, Harvard Medical School; Pathologist, Brigham and Women's Hospital, Boston, MA
The Breast

Martin C. Mihm, Jr., M.D.
Clinical Professor of Pathology, Harvard Medical School; Senior Dermatopathologist, Massachusetts General Hospital, Boston, MA
The Skin

Richard N. Mitchell, M.D., Ph.D.
Assistant Professor of Pathology, Harvard Medical School; Pathologist, Brigham and Women's Hospital, Boston, MA
Hemodynamic Disorders, Thrombosis, and Shock

George F. Murphy, M.D.
Professor of Pathology, Jefferson Medical College; Director of Cutaneous Pathology and Medical Education, Department of Pathology, Thomas Jefferson University, Philadelphia, PA
The Skin

Andrew Rosenberg, M.D.
Associate Professor of Pathology, Harvard Medical School; Associate Pathologist, Massachusetts General Hospital, Boston, MA
Bones, Joints, and Soft Tissue Tumors

John Samuelson, M.D., Ph.D.
Associate Professor, Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA
Infectious Diseases

Frederick J. Schoen, M.D., Ph.D.
Professor of Pathology, Harvard Medical School; Director, Cardiac Pathology, and Vice-Chairman, Department of Pathology, Brigham and Women's Hospital, Boston, MA
Blood Vessels; The Heart

Deborah Schofield, M.D., M.B.A.
Associate Professor of Pathology, University of Southern California; Attending Pathologist, Children's Hospital of Los Angeles, Los Angeles, CA
Diseases of Infancy and Childhood

Preface

We present this sixth edition of *Robbins Pathologic Basis of Disease* with considerable excitement, for these are heady times for pathology as a science and medical practice.

The rapid, sometimes frenetic pace of the discovery of genes and molecules has had a profound impact on the core of the science of pathology—the study of the *pathogenesis* of disease. While much still needs to be uncovered to link abnormal genes and the expression of disease, gone are the times when the mechanisms of most diseases were "unknown," or "obscure" or "mysterious." Those of us who toiled with these unknowns found it exhilarating, in completing this revision, to witness this extraordinary change in virtually every field of pathology.

We thus have attempted to weave the new discoveries of mechanisms throughout the text, blending them with the classic morphologic descriptions and clinical manifestations of diseases. It was difficult, but essential, to avoid information overload by making distinctions between new but unproven hypotheses and fundamental discoveries that will stand the test of time. However, while the latter received more attention, unsolved problems have not been eliminated because of our conviction that textbooks must not only provide explanations but also cajole open minds to pursue the path of discovery. Indeed, although the torrent of new knowledge appears daunting, in many cases it simplifies the task of both authors and readers, because long and wordy speculations are replaced by concise and rational molecular explanations.

The molecular advances are also changing pathology as a medical practice. While morphology remains at the heart of diagnostic pathology, immunologic, cytogenetic, and molecular analyses of tissues and cells are increasingly becoming guides to render diagnoses, to assess prognosis, and to suggest therapy. A golden era for genetic pathology is at hand, and we attempt in the chapters on organ systems to present critical molecular analyses relevant to specific diseases or tumors.

Although new knowledge has meant extensive revision, our goals remain essentially the same.

- To integrate into the discussion of pathologic processes and disorders the newest established information available—morphologic and molecular.
- To organize the presentations into logical and uniform approaches, thereby facilitating readability, comprehension, and learning.
- Not to permit the book to become larger and more cumbersome, and yet to provide adequate discussion of the significant lesions, processes, and disorders, allotting space in proportion to their clinical and biologic importance.
- To place great emphasis on clarity of writing and good usage of language in the recognition that struggling to comprehend is time-consuming and wearisome and gets in the way of the learning process.
- To make this first and foremost a student text—used by students throughout their four years of medical school and into their residencies—but, at the same time, to provide sufficient detail and depth to meet the needs of more advanced readers.

We hope that we have in some measure achieved these goals in a manner that will keep this text useful into the next millennium.

The basic organization of the book also remains largely unchanged. The chapters on general principles and processes, such as cell injury and inflammation, are confined to the first part of the text, while the remainder of the book is concerned with the disorders of various organs and systems. Every chapter has been carefully updated, and many have been largely rewritten. The previous Chapter 1, which included both cell injury and adaptations, has been divided into two chapters. The first includes a more thorough discussion of cell death and the expanded understanding of apoptosis and its role in disease. The second considers the

important adaptations, the intracellular accumulations, and recent insights into the mechanisms of cell aging. In systemic pathology, emphasis has remained on the origins of functional and structural changes, but the essential morphology, highlighted by a shaded background, has been carefully preserved. Whenever appropriate, genetic techniques relevant to the identification of particular lesions or tumors have been incorporated. The clinical significance of these changes has been integrated throughout the text.

In addition to revisions in text, there have been extensive changes in the illustrative material. Virtually all black and white photographs have been replaced by those in color. A large number of new schematics and diagrams that provide a three-dimensional view of cells and tissues have also been incorporated, but only where they can illuminate the text. We hope that this new infusion not only reinforces the textual matter but also makes the reading more pleasurable.

A liberal but judicious number of references are incorporated into the writing to provide source material for those who wish to pursue subjects of their own interest. Great effort was made in selecting these references for their quality, authenticity, and completeness. Most are recent—indeed some appeared in 1998—but older classics have been retained precisely because they are "classic."

While welcoming a new coauthor, Dr. Tucker Collins, and two additional chapter contributors to this edition, the senior authors reviewed, edited, and critiqued all of the chapters to ensure uniformity of style and flow that have been the hallmarks of this text. The authors were greatly helped by the advice and reviews of many experts who were sought out to confirm the accuracy, completeness, and authenticity of areas of their expertise, as detailed in the Acknowledgments section.

We hope that we have succeeded in transmitting to the readers of this text the beauty of the expanding knowledge of the nature of many diseases and have stimulated them to learn more about the pathologic basis of disease.

RSC

VK

TC

Acknowledgments

No textbook of this size can be completed without the help of many, many individuals. Hence, thanks and gratitude are owed to all of them for help in various ways in the completion of this edition.

First and foremost, all three of us wish to offer a salute to Dr. Stanley Robbins, who conceived this book and nourished it for more than 40 years. His principles of emphasizing clear writing and his uncompromising standards of accuracy continue to guide us. His mark on this book remains indelible. Second, we thank our contributing authors, trusted colleagues who have added to the luster of this book by preparing chapters in their areas of expertise. Their names appear in the Table of Contents and in the chapters themselves, and so it suffices here to note our gratitude to them for their willingness to lend their names and writing to this edition.

We also wish to acknowledge, with enormous gratitude, consultant colleagues who are not named as authors but who have reviewed, criticized, and sometimes even rewritten sections of this book in their specialty areas. Such excellence as the book may have is owed in part to them; any errors are ours. Foremost among those were:

- Dr. Manjeri Venkatachalam (Chapter 1—Cell Injury)
- Dr. Louis Picker (Chapter 3—Inflammation)
- Dr. Patricia D'Amore (Chapter 4—Tissue Repair)
- Dr. Nancy Schneider (Chapter 6—Genetic Disorders)
- Dr. Brian Dawson (Chapter 6—Genetic Disorders)
- Dr. William Edwards (Chapter 13—The Heart)
- Dr. Jon Aster (Chapter 14—Red Cells)
- Dr. David Dorfman (Chapter 15—The Thymus)
- Dr. Steven Kroft (Chapter 15—White Cells)
- Dr. David Sacks (Chapter 20—Diabetes)
- Dr. Helmut Rennke (Chapter 21—The Kidney)
- Dr. Andrew Renshaw (Chapter 22—Lower Urinary Tract)
- Dr. William Murphy (Chapter 22—Lower Urinary Tract)
- Dr. Dennis Burns (Chapter 26—Endocrine System)
- Dr. Christopher Fletcher (Surgical Pathology, several chapters)

Many other colleagues made their contributions by providing oversight and critiques in their special areas of interest or personal insights that influenced our writing. We particularly thank Drs. Abul Abbas, Amin Arnaout, Alan Beggs, Steven Blacklow, Carsten Bönnemann, Jonathan Epstein, David Genest, Robert Handin, Donald Ingber, David Louis, Richard Mitchell, James Morris, George Mutter, William Schoene, Charles Serhan, Mark Tanter, F.S. Vogel, Xiaodong Wang, Gayle Winters, and Ms. Nancy L. Robinson.

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We are also indebted to our publisher, W.B. Saunders Company, and the many in the company who participated

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And finally, once again we acknowledge our wives, Kerstin Cotran, Raminder Kumar, and Mary Whitley, for their tolerance of our absences and their unflinching support of this seemingly endless task.

RSC

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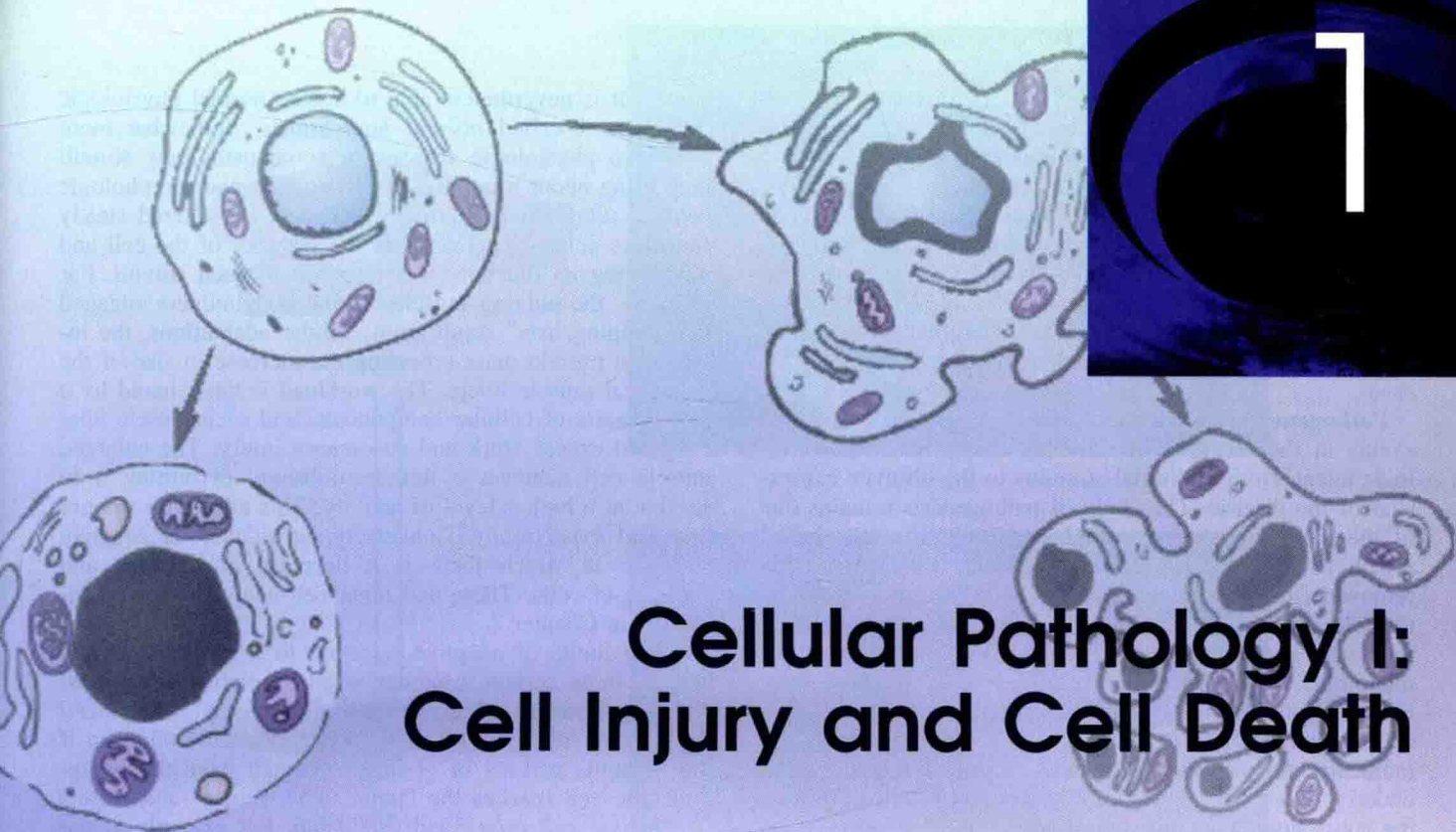
Contents

GENERAL PATHOLOGY

DISEASES OF ORGAN SYSTEMS



1

Cellular Pathology I: Cell Injury and Cell Death

INTRODUCTION TO PATHOLOGY

Pathology is literally the study *(logos)* of suffering *(pathos).* More specifically, it is a bridging discipline involving both basic science and clinical practice and is devoted to the study of the structural and functional changes in cells, tissues, and organs that underlie disease. By the use of molecular, microbiologic, immunologic, and morphologic techniques, pathology attempts to explain the whys and wherefores of the signs and symptoms manifested by patients while providing a sound foundation for rational clinical care and therapy.

Traditionally, the study of pathology is divided into general pathology and special or systemic pathology. The former is concerned with the basic reactions of cells and tissues to abnormal stimuli that underlie all diseases. The latter examines the specific responses of specialized organs and tissues to more or less well defined stimuli. In this book, we first cover the principles of general pathology and then proceed to specific disease processes as they affect particular organs or systems.

The four aspects of a disease process that form the core of pathology are its cause *(etiology),* the mechanisms of its development *(pathogenesis),* the structural alterations induced in the cells and organs of the body *(morphologic changes),* and the functional consequences of the morphologic changes *(clinical significance).*

Etiology or Cause. The concept that certain abnormal symptoms or diseases are "caused" is as ancient as recorded history. For the Arcadians (2500 B.C.), if someone became ill, it was the patient's own fault (for having sinned) or the makings of outside agents, such as bad smells, cold, evil spirits, or gods.[1] In modern terms, there are the two major classes of etiologic factors: intrinsic or

genetic and acquired (e.g., infectious, nutritional, chemical, physical). Knowledge or discovery of the primary cause remains the backbone on which a diagnosis can be made, a disease understood, or a treatment developed. The concept, however, of one etiologic agent to one disease—developed from the study of infections or single-gene disorders—is no longer sufficient. Genetic factors are clearly involved in some of the common environmentally induced maladies, such as atherosclerosis and cancer, and the environment may also have profound influences on certain genetic diseases.

Pathogenesis. Pathogenesis refers to the sequence of events in the response of the cells or tissues to the etiologic agent, from the initial stimulus to the ultimate expression of the disease. The study of pathogenesis remains one of the main domains of pathology. Even when the initial infectious or molecular cause is known, it is many steps removed from the expression of the disease. For example, to understand cystic fibrosis is to know not only the defective gene and gene product but also the biochemical, immunologic, and morphologic events leading to the formation of cysts and fibrosis in the lung, pancreas, and other organs. Indeed, as we shall see throughout the book, the molecular revolution has already identified mutant genes underlying a great number of diseases and promises to map the entire human genome before too long. Nevertheless, the functions of the encoded proteins and how mutations induce disease are often still obscure. Thus, the study of pathogenesis has never been more exciting scientifically or more relevant to the development of new therapies.

Morphologic Changes. The morphologic changes refer to the structural alterations in cells or tissues that are either characteristic of the disease or diagnostic of the etiologic process.

Functional Derangements and Clinical Significance. The nature of the morphologic changes and their distribution in different organs or tissues influence normal function and determine the clinical features (symptoms and signs), course, and prognosis of the disease.

Virtually all forms of organ injury start with molecular or structural alterations in *cells*, a concept first put forth in the 19th century by Rudolf Virchow, known as the father of modern pathology. We therefore begin our consideration of pathology with the study of the origins, molecular mechanisms, and structural changes of cell injury. Yet different cells in tissues constantly interact with each other, and an elaborate system of *extracellular matrix* is necessary for the integrity of organs. Cell-cell and cell-matrix interactions contribute significantly to the response to injury, leading collectively to *tissue* and *organ injury*, which are as important as cell injury in defining the morphologic and clinical patterns of disease.[2]

DEFINITIONS

The normal cell is confined to a fairly narrow range of function and structure by its genetic programs of metabolism, differentiation, and specialization; by constraints of neighboring cells; and by the availability of metabolic substrates. It is nevertheless able to handle normal physiologic demands, so-called *normal homeostasis*. Somewhat more excessive physiologic stresses or some pathologic stimuli may bring about a number of physiologic and morphologic *cellular adaptations*, during which new but altered steady states are achieved, preserving the viability of the cell and modulating its function as a response to such stimuli. For example, the bulging muscles of the bodybuilders engaged in "pumping iron" result from cellular adaptations, the increase in muscle mass reflecting the increase in size of the individual muscle fibers. The workload is thus shared by a greater mass of cellular components, and each muscle fiber is spared excess work and so escapes injury. The enlarged muscle cell achieves a new equilibrium, permitting it to survive at a higher level of activity. This adaptive response is called *hypertrophy*. Conversely, *atrophy* is an adaptive response in which there is a decrease in the size and function of cells. These and other cell adaptations are considered in Chapter 2.

If the limits of adaptive response to a stimulus are exceeded, or in certain instances when adaptation is not possible, a sequence of events follows, loosely termed *cell injury*. Cell injury is *reversible* up to a certain point, but if the stimulus persists or is severe enough from the beginning, the cell reaches the "point of no return" and suffers *irreversible cell injury* and *cell death*. For example, if the blood supply to a segment of the heart is cut off for 10 to 15 minutes and is then restored, the myocardial cells experience injury but can recover and function normally. If blood flow is not restored until 1 hour later, however, irreversible injury ensues, and many myocardial fibers die. *Adaptation, reversible injury, irreversible injury*, and *cell death* can be considered states of progressive encroachment on the cell's normal function and structure (Fig. 1–1).

Cell death, the ultimate result of cell injury, is one of the most crucial events in pathology, affecting every cell type and being the major consequence of ischemia (lack of blood flow), infection, toxins, and immune reactions. In addition, it is critical during normal embryogenesis, lymphoid tissue development, and hormonally induced involution and is the aim of cancer radiotherapy and chemotherapy.

There are two principal patterns of cell death, *necrosis* and *apoptosis*.[2]

- *Necrosis* or *coagulation necrosis* is the more common type of cell death after exogenous stimuli, occurring after such stresses as ischemia and chemical injury. It is manifested by severe cell swelling or cell rupture, denaturation and coagulation of cytoplasmic proteins, and breakdown of cell organelles.
- *Apoptosis* occurs when a cell dies through activation of an internally controlled suicide program. It is a subtly orchestrated disassembly of cellular components designed to eliminate unwanted cells during embryogenesis and in various physiologic processes. Doomed cells are removed with minimum disruption to the surrounding tissue. It also occurs, however, under pathologic conditions, in which it is sometimes accompanied by necrosis. Its chief morphologic features are chromatin condensation and fragmentation. Although the mechanisms of necrosis and apoptosis differ, as we shall see, there is